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Inflammatory pseudotumor of the liver occurring during the course of hepatitis C virus-related hepatocellular carcinoma treatment: A case report

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ABSTRACT

INTRODUCTION: Inflammatory pseudotumor (IPT) of the liver is a rare and benign disease that has a good prognosis. It is often difficult to distinguish IPT from hepatic malignancies, such as hepatocellular carcinoma (HCC), because specific clinical symptoms are absent and the diseases' radiological findings can be similar. IPT is particularly difficult to distinguish from HCC in livers with hepatitis C virus (HCV)-related cirrhosis. We report a case of IPT of the liver that mimicked HCV-related HCC recurrence.
PRESENTATION OF CASE: A 78-year-old asymptomatic Japanese man who had undergone hepatectomy for HCV-related HCCs (moderately differentiated type) in segments 7 and 5 four and a half years previously was referred to our hospital for treatment of a 30-mm enhanced tumor in segment 5 (a typical HCC pattern). The tumor was identified via abdominal dynamic computed tomography (CT) and CT with hepatic arteriography and arterial portography. Thereafter, liver segmentectomy 5 was performed, and the histopathological diagnosis was a 10-mm IPT of the liver. After 1.5 years, magnetic resonance imaging revealed two new enhanced lesions in segment 8, which showed the typical pattern of HCC. Because these lesions grew in size for 3 months, liver segmentectomy 8 was performed for HCC recurrence. Histopathological examination showed that both lesions were HCCs.
CONCLUSION: HCV-related HCC has a high rate of multicentric recurrence. Our experience suggests that, when a hepatic lesion is suspected to be HCC, surgical resection should be considered for curative treatment and to rule out malignancy, even if the lesion may be an IPT.

1. Introduction

Inflammatory pseudotumor (IPT) of the liver is a rare and benign lesion that has a good prognosis. IPT is characterized by chronic infiltration of inflammatory cells and areas of fibrosis [1,2]. The etiology of IPT remains uncertain, although infectious conditions, autoimmune phenomenon, and systemic inflammatory response syndrome have been suggested as possible causes [3–5]. As a consequence of similar radiological features, IPT of the liver is often difficult to differentiate from other malignant diseases, such as hepatocellular carcinoma (HCC) [6,7], intrahepatic cholangiocarcinoma [1,8], and metastatic tumor [9]. It is extremely difficult to establish an accurate preoperative diagnosis of IPT based on radiological imaging, particularly for cases in which IPT occurs in a liver that is affected by chronic viral hepatitis [6]. Here, we report a rare case of IPT of the liver that occurred during the course of treatment for hepatitis C virus (HCV)-related HCC.

2. Presentation of case

A 78-year-old Japanese man was referred to our hospital for treatment of a hepatic tumor in segment 5, which was identi-

Abbreviations: IPT, inflammatory pseudotumor; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; CT, computed tomography; CRP, C-reactive protein; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-2; SOL, space-occupying lesion; CTHA, CT hepatic arteriography; CTAP, CT during arterial portography; IgG4, immunoglobulin G4; MRI, magnetic resonance imaging; PET-CT, positron emission tomograph computed tomography; SUVmax, maximum standardized uptake value; ESR, erythrocyte sedimentation rate.

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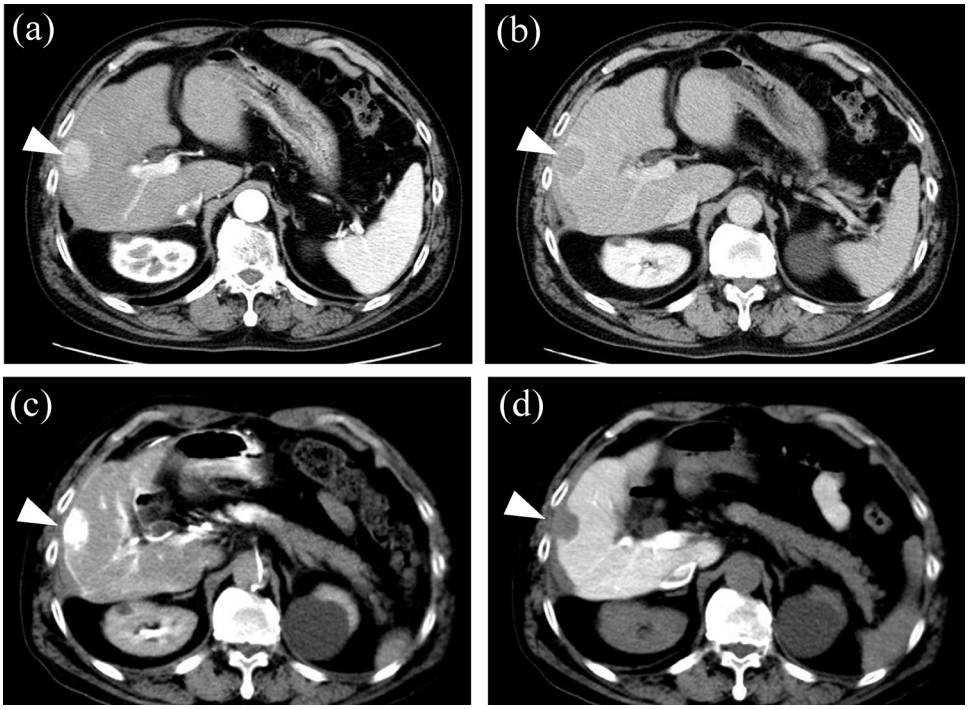

Fig. 1. Abdominal dynamic computed tomographic (CT) image showing a 30-mm space-occupying lesion (arrowhead) in segment 5 of the liver, which was visible as a homogeneously enhanced lesion at an early phase (a), and was washed out at a late phase (b). CT during hepatic arteriography revealed a hypervascular tumor (c), and CT during arterial portography revealed a perfusion defect (d). No other tumors were found in the examination.

fied via abdominal computed tomography (CT), although he had no complaints or symptoms. Four and a half years prior, he had undergone hepatectomy for HCCs (moderately differentiated type) in segments 7 and 5; the operation consisted of segmentectomy 7, wedge resection in segment 5, and cholecystectomy (first operation). The patient had been positive for HCV antibody and negative for HCV-RNA without interferon based therapy.

In laboratory studies, no inflammatory response was observed, the white blood cell count was 5060/mm^3, and the C-reactive protein (CRP) level was 0.16 mg/dL. Additional laboratory results were as follows: total bilirubin, 1.1 mg/dL; aspartate aminotransferase, 26 IU/L; alanine aminotransferase, 21 IU/L; alkaline phosphatase, 266 IU/L; and γ-glutamyl transpeptidase, 39 IU/L. Levels of alpha-fetoprotein (AFP; 5.7 ng/mL) and protein induced by vitamin K absence-2 (PIVKA-II; 13 mAU/mL) were within their normal limits.

Abdominal dynamic CT revealed a 30-mm contrast-enhanced space-occupying lesion (SOL) in segment 5 at an early phase. The lesion presented with washout at a late phase (Fig. 1a, b). CT hepatic arteriography (CTHA) was performed to allow more detailed examination, revealing a hypervascular tumor. Further, CT during arterial portography (CTAP) revealed a perfusion defect in segment 5 (Fig. 1c, d).

The tumor in segment 5 was diagnosed as an HCC recurrence based on radiological findings, as it showed the typical pattern of moderately differentiated HCC. Segmentectomy 5 was therefore performed (a second operation). Histopathological examination revealed inflammatory granulation tissue in a 10-mm yellow-brown nodular lesion. The final diagnosis was IPT of the liver (Fig. 2). Infiltrating plasma cells were positive for immunoglobulin G4 (IgG4) on immunohistochemistry. The nontumor area of the specimen showed chronic hepatitis, as indicated by slight lymphocyte permeation around the portal vein.

The subsequent follow-up was conducted using contrast-enhanced magnetic resonance imaging (MRI) because a contrast-enhanced CT had caused allergic symptoms after the second operation. One year and 6 months following the second surgery, two new lesions appeared in segment 8. Abdominal contrast-enhanced MRI revealed a tumor (diameter, 16 mm) near the border of segment 8 and a tumor (diameter, 10 mm) below the hepatic dome. Both tumors showed contrast enhancement at the arterial phase and washout at the hepatic cell phase. In a follow-up MRI that was performed 3 months later, the tumor near the border of segment 8 was observed to have grown from 16 to 20 mm, and the tumor below the hepatic dome was observed to have grown from 10 to 17 mm (Fig. 3). Sonazoid-enhanced ultrasonography showed the tumor near the border of segment 8 as a 15-mm hyperechoic lesion at the early vascular phase, as well as a defect lesion at the late Kupffer phase. Positron emission tomography/computed tomography (PET-CT) revealed uptake in the lesion near the border of segment 8, with a maximum standardized uptake value (SUVmax) of 5.0 mC/kg body weight. Further, PET-CT showed uptake in the lesion below the hepatic dome, with an SUVmax of 2.9 mC/kg. The levels of tumor markers AFP and PIVKA-II were within the normal limits during follow-up.

Because HCC recurrence was strongly suspected, liver segmentectomy 8 was performed (a third operation), including the two growing lesions. Histopathological examination determined that both lesions in segment 8 were HCCs (moderately differentiated type). The nontumor area of the specimen showed necrotic inflammatory reactions with bridging fibrosis and bridging necrosis around the portal vein. Currently, at 2 years after the most recent surgery, the patient has shown no recurrence.

3. Discussion

IPT of the liver was first described by Pack and Baker in 1953 [10]. Since the first report of this rate entity, more than 200 cases of IPT of the liver have been reported in the English literature [11]. However, the etiology of IPT remains unknown. Some cases have been associated with abscess formation [12], bacterial infection [4], autoimmune reactions [3], and viral infections, such as with hepatitis B virus [11], HCV [7,13], and Epstein-Barr virus [14]. It has led

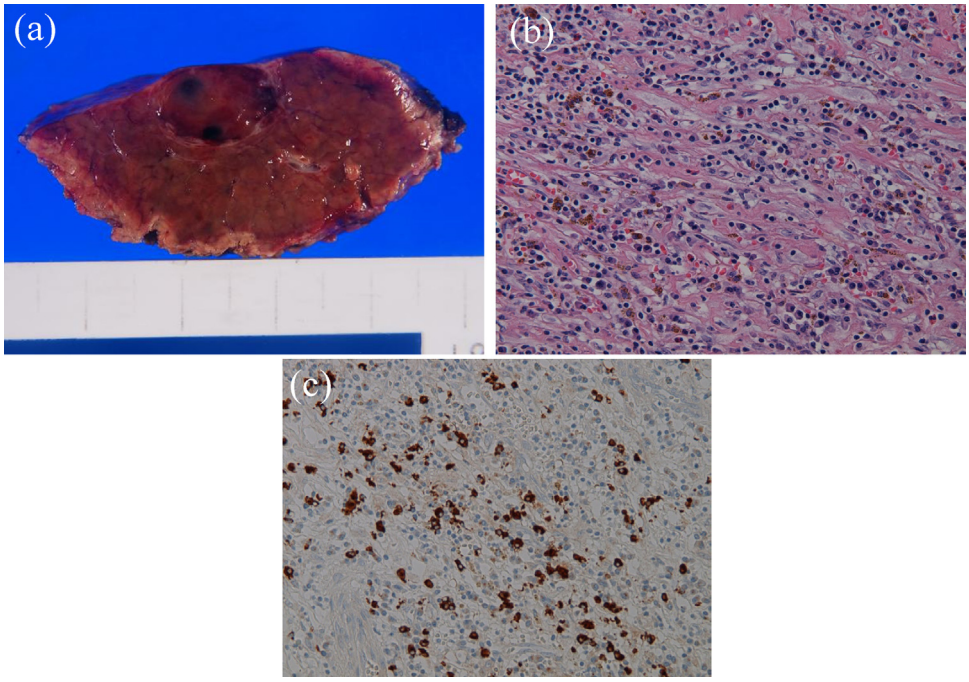

Fig. 2. Cut surface of the resected specimen showing a 10- × 10-mm yellow-brown nodular lesion (a). The histopathological finding showed fibrosis and numerous infiltrating lymphocytes and plasma cells in the tumor (b: hematoxylin and eosin stain, ×400). Many infiltrating plasma cells were positive for IgG4 (c: on immunohistochemistry, ×400).

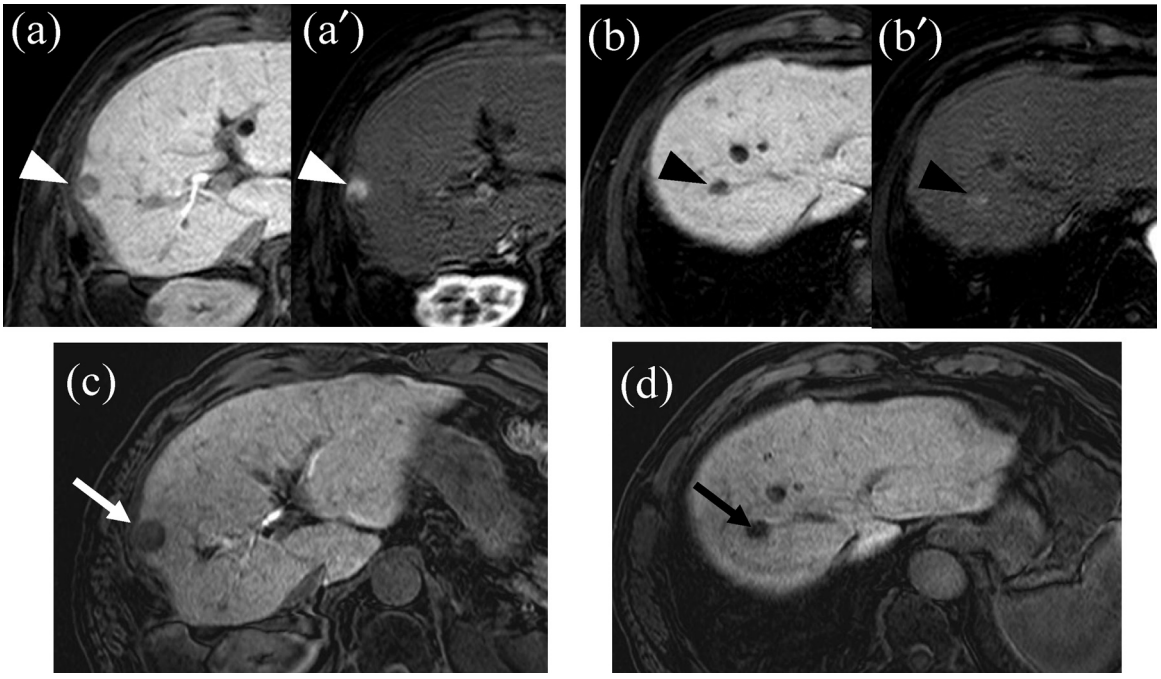

Fig. 3. Contrast-enhanced magnetic resonance image (MRI) showing two new lesions with perfusion defect at the hepatic cell phase and good enhancement at the arterial phase. The white arrowhead indicates the 16-mm tumor near the border of segment 8 (a: hepatic cell phase, a′: arterial phase). The black arrowhead indicates the 10-mm tumor below the hepatic dome in segment 8 (b: hepatic cell phase, b′: arterial phase). The follow-up MRI scan obtained 3 months later shows that the tumor near the border of segment 8 had grown to 20 mm (c: white arrow) and that the lesion below the hepatic dome had grown to 17 mm (d: black arrow).

to the suggestion that IPTs of the liver may be caused by any local or systemic inflammatory reactions.

In several retrospective reports, IPTs of the liver were frequently associated with symptoms such as abdominal pain, fever, malaise, and weight loss; nonetheless, the percentage of asymptomatic cases was not small [15–17]. The most common abnormal laboratory findings were an increased serum erythrocyte sedimentation rate (ESR) and/or CRP level. In the present case, the CRP level was not elevated and was within the normal range before the second

operation. However, the ESR was not surveyed during the follow-up period.

The present case was completely asymptomatic, and was identified through an incidental CT finding during follow-up for HCC. The patient had not had any recent episode of bacterial infection, such as with cholangitis. We regarded the inflammatory reactions to HCV activity as the cause of IPT in this case. Unlike the disease status at the second operation, the histopathological characteristics, HCV activity, and fibrosis in the nontumor area were observed to be progressive at the third operation. Thus, we speculated that latent but active hepatitis had actually been present, despite the negative HCV-RNA test result. To the best of our knowledge, IPT after HCV infection has only been described in two cases in the English literature. Both cases were originally suspected to be HCC and were finally diagnosed as IPT based on liver biopsy findings. However, the specific mechanisms of IPT development after HCV infection were not discussed [7,13]. IgG4-positive infiltrating plasma cells were observed in the pseudotumor on immunohistochemistry, indicating the possibility of IgG4-related disease. IgG4-related disease is characterized by abundant IgG4-positive plasma cell infiltration and a high serum IgG4 level [3]. Hepatic IPTs with IgG4-related disease are usually associated with sclerosing cholangitis. In the present case, no clinical or histopathological evidence of sclerosing cholangitis was found, and the serum IgG4 level was 30.3 mg/dL, which is within the normal range (4.8–105.0 mg/dL). Thus, this case was unlikely to have been IgG4-related disease. Instead, it is more likely to have been a nonspecific IPT that included numerous IgG4-positive plasma cells.

To date, two cases of IPT with synchronous HCC have been reported. One case involved co-localization of IPT and HCC in the liver of a patient with alcoholic hepatitis [18], while the other case was only identified intraoperatively in a patient with hepatitis B virus-related HCC [2]. The occurrence of IPT with asynchronous HCC during the course of HCC treatment has not been reported previously. HCV-related HCC is widely known to have a high multicentric occurrence rate. It is extremely difficult to obtain an accurate preoperative diagnosis of IPT that occurs during HCC treatment, and resection of the lesion is appropriate. In the present case, we observed bridging fibrosis and necrosis of the nontumor area of the specimen from the third operation, suggesting the possibility of HCC recurrence in the future.

According to previous reports, IPTs have had an indefinite appearance in radiological examinations [5,19]. In the present case, the IPT showed the typical pattern of moderately differentiated HCC. When a hepatic mass has been diagnosed as HCC according to radiographic findings, resection of the lesion is usually selected without fine-needle biopsy, to prevent the risk of neoplastic seeding or morbidity such as bleeding.

The appropriate treatment protocol for IPT is uncertain, and the management of IPT is controversial [2,6]. Conservative treatments with antibiotics or nonsteroidal anti-inflammatory drugs have been reported in some cases that included tumor regression. In the present case, the tumor diameter was 30 mm at the preoperative diagnosis, although regression to 10 mm was observed in the resected specimen from the second operation. If a follow-up examination had been performed just prior to the second operation, the extent of regression might have been observed. However, rapid treatment was required because the treatment target was malignant disease. Before the third operation, twice contrast-enhanced MRI, contrast ultrasonography, and PET-CT scan were performed to improve the precision of the preoperative diagnosis. Based on the imaging results, the resected lesions were considered to be HCC recurrences. Thus, curative resection was performed to avoid missing the operable period. IPTs that are treated conservatively have a potential for metastasis, and the co-localization of IPT and HCC has been reported [18]. Surgical resection is needed, both for curative treatment and to rule out malignancy.

4. Conclusion

We have reported a rare case of IPT of the liver that occurred during the course of HCV-related HCC treatment. When a hepatic lesion is suspected to be HCC, surgical resection should be considered for curative treatment and to rule out malignancy, even if the lesion may be an IPT.

Conflict of interest

None of the authors has anything to disclose.

Funding

None of the authors has anything to disclose.

Ethical approval

All procedures used in this research were approved by the Ethical Committee of Hiroshima University Hospital.

Consent

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of the written consent form is available for review by the Editor-in-Chief of this journal.

Authors' contributions

Honmyo, Kuroda, Kobayashi, and Ohdan were responsible for the conception and design of this study. Ishiyama, Ide, Tahara, and Ohira participated in the data acquisition. Honmyo, Kuroda, Kobayashi, Tashiro, and Ohdan performed the analysis and interpretation of the data. Kuroda and Kobayashi helped to draft the manuscript. Arihiro analyzed the pathological findings. Kuroda, Kobayashi, and Ohdan coordinated the study and critically revised the manuscript. All of the authors read and approved the final manuscript.

Guarantor

Tsuyoshi Kobayashi has accepted full responsibility for this work and the decision to publish it.

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